# Orchard Therapeutics Receives U.S. FDA Fast Track Designation for OTL-203 in MPS-IH

November 30, 2023

*Previously reported results from ongoing proof-of-concept study showed extensive metabolic correction, continued cognitive, motor, and physical development, as well as early improvements in skeletal health*

*Additionally, study investigators presented favorable outcomes for other disease manifestations not effectively addressed by the current standard of care at ESGCT 2023*

*Global registrational trial expected to commence by year-end*

BOSTON and LONDON, Nov. 30, 2023 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced the U.S. Food and Drug Administration (FDA) has granted Fast Track designation to OTL-203, an investigational hematopoietic stem cell gene (HSC) therapy being developed for the potential treatment of the Hurler subtype of mucopolysaccharidosis type I (MPS-IH). Fast Track designation is intended to expedite the development of promising medicines that address serious medical needs. Therapeutic candidates that receive Fast Track designation may be eligible for enhanced interactions with the FDA, including potentially quicker submission and review timelines.

MPS-I is a rare, inherited neurometabolic disease caused by a deficiency of the alpha-L-iduronidase (IDUA) lysosomal enzyme resulting in the accumulation of glycosaminoglycans (GAGs) in multiple organs, including the eyes, ears, heart, as well as the musculoskeletal and central nervous systems. It is estimated to occur globally in 1 in 100,000 live births. Approximately 60 percent of children born with MPS-I have the most severe subtype, MPS-IH, also called Hurler syndrome, and rarely live past the age of 10 when untreated. Current treatment options for MPS-IH include allogeneic hematopoietic stem cell transplant (HSCT) and chronic enzyme replacement therapy (ERT), both of which have significant limitations.

“At Orchard Therapeutics, we are applying our HSC gene therapy platform to indications where we believe it is clinically differentiated and has the greatest potential to make a paradigm-shifting impact on the treatment landscape,” said Leslie Meltzer, Ph.D., chief medical officer. “We are encouraged that OTL-203 has been granted Fast Track designation because new treatment options are urgently needed for children with MPS-IH, as the current standard of care is associated with significant morbidity and mortality. Moreover, existing treatment options do not adequately address the broad range of clinical manifestations of the disease, including those that are most burdensome and have a high impact on quality of life. We look forward to initiating our global registrational trial in December to evaluate the efficacy and safety of OTL-203 compared to allogeneic HSCT.”

OTL-203 has previously received Rare Pediatric Disease (RPD) and priority medicines (PRIME) designations from the FDA and European Medicines Agency, respectively.

***Summary of the Clinical Development Program for OTL-203***

In an ongoing single-center proof-of-concept (PoC) study, eight patients diagnosed with MPS-IH were treated at Ospedale San Raffaele in Milan, Italy with investigational OTL-203 between July 2018 and December 2019. Interim results published in *The New England Journal of Medicine* showed all patients had stable cognitive performance post-treatment. In addition, all participants had progressed along expected growth percentiles of healthy children and exhibited longitudinal growth that was considered within the normal range adjusted for age and gender. In subsequent follow-up, study investigators have observed continued cognitive development and evidence of continued growth within normal range and improvements in skeletal health with a median follow-up of 3.78 years (range: 3.14 to 4.58 years) as of May 2023.

In addition to the biochemical, neurological and skeletal results previously reported, last month at the European Society of Cell and Gene Therapy (ESGCT) 30th Annual Congress, Dr. Maria Ester Bernardo, clinical coordinator, pediatric clinical research unit at San Raffaele Telethon-Institute for Gene Therapy (SR-TIGET) and the principal investigator of the PoC study, detailed the first findings on other treatment outcomes, including ocular (eye) symptoms and auditory (hearing) function. Results showed favorable results for disease manifestations not effectively addressed by the current standard of care and further highlights the ability of gene modified HSCs to migrate into and correct abnormalities in multiple different tissues and organs.

Throughout the PoC study, treatment with OTL-203 has been generally well-tolerated with a safety profile consistent with the selected conditioning regimen. The viral vector integration profile was consistent with other lentiviral-based HSC gene therapy studies, and all participants had a stable and highly polyclonal repertoire. Anti-alpha-L-iduronidase (IDUA) antibodies present prior to gene therapy as a result of ERT were not seen in any patient within two months following treatment. In addition, ERT was discontinued at least three weeks prior to any patient receiving gene therapy treatment, and no patients have re-started ERT post-treatment.

***Global Registrational Trial Expected to Commence by Year-end***

Following the promising results observed in the PoC study, Orchard Therapeutics is initiating a multi-center, randomized, active controlled clinical trial designed to evaluate the efficacy and safety of OTL-203 in patients with MPS-IH compared to standard of care with allogeneic HSCT. A total of 40 patients with a confirmed diagnosis of MPS-IH who meet the study inclusion criteria will be randomized 1:1 to receive either OTL-203 or allogeneic HSCT. The study is powered to demonstrate superiority of OTL-203 over HSCT.

The primary endpoint, which will be measured at two years post-treatment, comprises a composite of clinically meaningful outcomes, including death, the need for rescue transplant, treatment failure, immunological complications, as well as severe cognitive and/or growth impairment. Secondary endpoints include biochemical markers, additional clinical assessments, as well as safety and tolerability. The company expects to activate up to six sites in the United States and Europe. For more information, please visit www.clinicaltrials.gov (NCT06149403).

**About MPS-I**
Mucopolysaccharidosis type I (MPS-I) is a rare, inherited neurometabolic disease caused by a deficiency of the alpha-L-iduronidase (IDUA) lysosomal enzyme, which is required to break down sugar molecules called glycosaminoglycans (GAGs). The accumulation of GAGs across multiple organ systems results in multiple symptomatic manifestations of the disease including severe neurocognitive impairment, skeletal deformities, cardiovascular and pulmonary complications, impaired motor function, loss of hearing and corneal clouding. MPS-I occurs at an overall estimated frequency of one in every 100,000 live births. There are three subtypes of MPS-I. Approximately 60 percent of children born with MPS-I have the most severe subtype, called Hurler syndrome (MPS-IH), and rarely live past the age of 10 when untreated.

Treatment options for MPS-I include hematopoietic stem cell transplant and chronic enzyme replacement therapy, both of which have limitations, such as inadequate impact on some of the more severe manifestations of disease, as well as significant morbidity and mortality. At present, Newborn Screening (NBS) for MPS-I has been established in multiple geographies, including the United States and Europe.

**About OTL-203**
OTL-203 is an investigational hematopoietic stem cell gene therapy being developed for the treatment of MPS-IH. It uses a modified virus to insert a functional copy of the *IDUA* gene into a patient's cells. OTL-203 is being developed in partnership with the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy. OTL-203 has received Rare Pediatric Disease (RPD) and Fast Track designations from the U.S. FDA, as well as priority medicines (PRIME) status from the European Medicines Agency.

**About Orchard Therapeutics**
At Orchard Therapeutics, our vision is to end the devastation caused by genetic and other severe diseases. We aim to do this by discovering, developing and commercializing new treatments that tap into the curative potential of hematopoietic stem cell (HSC) gene therapy. In this approach, a patient's own blood stem cells are genetically modified outside of the body and then reinserted, with the goal of correcting the underlying cause of disease in a single treatment.

In 2018, the company acquired GSK's rare disease gene therapy portfolio, which originated from a pioneering collaboration between GSK and the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy. Today, Orchard is advancing a pipeline spanning pre-clinical, clinical and commercial stage HSC gene therapies designed to address serious diseases where the burden is immense for patients, families and society and current treatment options are limited or do not exist.

Orchard has its global headquarters in London and U.S. headquarters in Boston. For more information, please visit www.orchard-tx.com, and follow us on X (formerly Twitter) and LinkedIn.

**Availability of Other Information About Orchard**
Investors and others should note that Orchard communicates with its investors and the public using the company website (www.orchard-tx.com), the investor relations website (ir.orchard-tx.com), and on social media (X; formerly Twitter and LinkedIn), including but not limited to investor presentations and investor fact sheets, U.S. Securities and Exchange Commission filings, press releases, public conference calls and webcasts. The information that Orchard posts on these channels and websites could be deemed to be material information. As a result, Orchard encourages investors, the media, and others interested in Orchard to review the information that is posted on these channels, including the investor relations website, on a regular basis. This list of channels may be updated from time to time on Orchard's investor relations website and may include additional social media channels. The contents of Orchard's website or these channels, or any other website that may be accessed from its website or these channels, shall not be deemed incorporated by reference in any filing under the Securities Act of 1933.

**Forward-looking Statements**
This press release contains forward-looking statements, which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Forward-looking statements include express or implied statements relating to, among other things, the therapeutic potential of OTL-203, the development timeline for OTL-203, including the timing of clinical trials, and the timing and likelihood of regulatory approvals for OTL-203. These statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, many of which are beyond Orchard's control, which could cause actual results to differ materially from those contemplated in these forward-looking statements. In particular, these risks and uncertainties include, without limitation, the risk that the development of OTL-203 will be delayed, the risk that OTL-203 will not be successfully approved or commercialized and the risk that long-term adverse safety findings may be discovered. Given these uncertainties, the reader is advised not to place any undue reliance on such forward-looking statements.

Other risks and uncertainties faced by Orchard include those identified under the heading "Risk Factors" in Orchard's most recent annual or quarterly report filed with the U.S. Securities and Exchange Commission (SEC), as well as subsequent filings and reports filed with the SEC. The forward-looking statements contained in this press release reflect Orchard's views as of the date hereof, and Orchard does not assume and specifically disclaims any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

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